REMARKS

Claims 1-11 are pending in this application. No amendments to the claims are entered in this paper. Applicants respectfully request reconsideration of the claims in view of the remarks provided below.

Claim Rejections under 35 U.S.C. § 103

Claims 1 and 3-10 have been rejected under 35 U.S.C. § 103(a) as unpatentable over WO 00/74489 to Sorensen et al. ('489 publication) in view of U.S. Patent No. 5,773,422 to Komer ('422 patent). The Examiner asserts that it would have been prima facie obvious to one of skill in the art to modify the teaching of the '489 publication to incorporate a pyrrolidone organic solvent based on the teaching of the use of pyrrolidone solvents in the '422 patent. Applicants respectfully disagree and traverse the rejection.

The '489 publication is directed to partitioned compositions (multiple phases) comprising a first active agent, including a macrocyclic lactone (ML), in a first organic liquid phase and a second active agent, particularly levamisole, in a second aqueous liquid phase (see abstract). The reference does not teach or suggest the use of a pyrrolidone solvent or that a ML and levamisole are both dissolved in a single solvent, as recited claim 1, which would bring the two active agents into a single phase. In fact, the '489 publication fairly teaches that in order to achieve stable compositions comprising a ML and levamisole, the two active agents must be separated from each other in their respective solvent systems by being present in different phases. For example, the '489 publication abstract states "*[t]he composition enables a chemically and physically stable anthelmintic composition to be prepared of at least two incompatible althelmintic actives (viz. A macrocyclic lactone (eg; ivermectin), and levamisole)* ..." Furthermore, page 3, lines 4-6 of the '489 publication states *"[d]espite combinations above being developed no stable ML anthelmintic and levamisole combination has been marketed. Previous attempts at such a combination resulted in unstable formulation – see our own Examples 1-6 hereafter."* The publication describes that MLs and levamisole require different environments, and that levamisole requires an acidic pH for stability (see page 1, lines 2-7).

The stable formulations described in the '489 publication that combine a ML and levamisole include two separate phases with each active agent in a different phase. The first

phase includes an organic carrier and the lipophilic ML and the second phase includes aqueous solvent having a pH of less than 7 that carries levamisole (see page 4, lines 5-21). It would be clear to one of skill in the art that since the ML resides in the organic phase and the levamisole resides in the aqueous phase, the two actives are separated by the partition of the two solvents. For example, the publication states on page 4, lines 8-12 "... *(i) at least one organic liquid carrier which carries at least most of the lipophilic active ingredient(s), thereby defining an organic liquid phase, ...(iv) at least water which carries at least most of said levamisole thereby defining an aqueous phase*, ..."

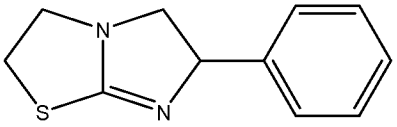
The Office Action cites Examples 1-4 of the '489 patent, which describe formulations containing abamectin and levamisole HCl together with various excipients and water. However, as noted above, the '489 publication states on page 3, lines 4-6, that Examples 1-6 of the publication demonstrate that previous combinations of a ML and levamisole resulted in unstable formulations. Examples 2-6 of the '489 publication (page 20, line 10 to page 23, line 26, describe formulations that comprise abamectin (ML) and levamisole with water and propylene glycol carriers, which exhibit unacceptable degradation of abamectin. Although the '489 publication states that formulation in Example 1 was physically stable, it does not provide any information on the chemical stability of the ML. Since the formulation of Example 2 contains the same components at the same concentrations (with the addition of 0.50% w/v cellulose gum CMC), one would also expect that the formulation of Example 1 would exhibit a similar degradation of abamectin. On page 22, lines 2-4, the '489 publication states *"[t]hese completely aqueous formulation approaches were then stopped and it was decided to use a vegetable oil to attempt to encapsulate the Abamectin and possibly protect it from the low pH of the water phase*." Therefore, the '489 publication fairly teaches that the ML and the levamisole must be in two different phases and separated from each other in order to achieve the desired stability. This teaches against inclusion of the two incompatible active agents in solution in a single solvent.

In contrast, claim 1 recites a stable formulation consisting essentially of levamisole and an avermectin or levamisole and a milbemycin dissolved in a pyrrolidone solvent. The formulation recited in the claims requires that both the ML active agent and levamisole are dissolved in the pyrrolidone solvent and that the formulation is stable. The surprising stability of the formulation recited in claim 1 is demonstrated by Study 11 on page 15, line 20 to page 16, line 22 of the specification. In contrast, the numerous formulations shown in Studies 1-10 on

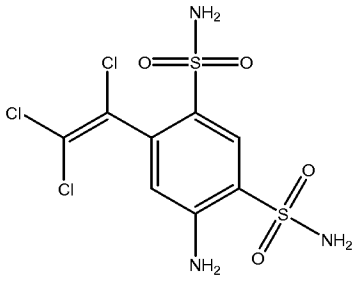
pages 6-15 of the specification exhibit unsuitable degradation of abamectin, demonstrating the difficulty in combining a ML and levamisole in a composition, consistent with Examples 1-6 of the '489 publication. The '489 publication does not teach or suggest the stable formulation of claim 1, which requires that both a ML and levamisole are present in a single phase dissolved in an organic pyrrolidone solvent. On the contrary, the '489 publication teaches away from the formulation of the invention because it describes that the ML and levamisole are incompatible and must be carried in different solvents that are not miscible to achieve a stable formulation.

The combination of the '422 patent with the teaching of the '489 publication does not teach or suggest the formulation recited in the claims. The '422 patent describes that avermectins are sufficiently soluble in N-methylpyrrolidone (NMP) and 2-pyrrolidone and that formulations comprising avermectin active agents and NMP, 2-pyrrolidione, or mixtures thereof, may be prepared for administration by intramuscular or subcutaneous injection, topical application, or oral administration. As noted previously, the '422 patent does not teach or suggest a combination of a ML together with levamisole. The '422 patent only teaches combinations of a ML with clorsulon in a pyrrolidone solvent. Furthermore, the '422 patent does not teach or suggest formulations comprising a milbemycin active agent with a pyrrolidone solvent.

The structures of clorsulon and levamisole are quite different, as shown below. As such, one of skill in the art would expect that the two active agents would have substantially different properties, including solubility and stability in organic and aqueous solvents.



levamisole



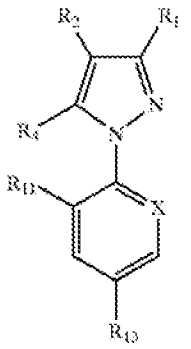
clorsulon

The description in the '422 patent that NMP or 2-pyrrolidone may be used in formulations comprising an avermectin alone or an avermectin in combination with clorsulon does not suggest that pyrrolidone solvents may be used to prepare stable formulations comprising a ML with levamisole, which is described in the '489 publication as having quite

different solubility characteristics and stability requirements (see page 1, lines 2-10). In contrast with the combination of a ML and clorsulon described in the '422 patent, the '489 publication clearly teaches that MLs are incompatible with levamisole, guiding away from combining the two active agents in the same solvent in a single phase. One of skill in the art, in view of the combined teachings of the '489 publication and the '422 patent would not have any expectation of success that a combination of a ML with levamisole in a single phase and solvent would produce a stable formulation. Therefore, Applicants respectfully submit that neither the '489 publication or the '422 patent alone or in combination render the claims obvious. Accordingly, withdrawal of the rejection is respectfully requested.

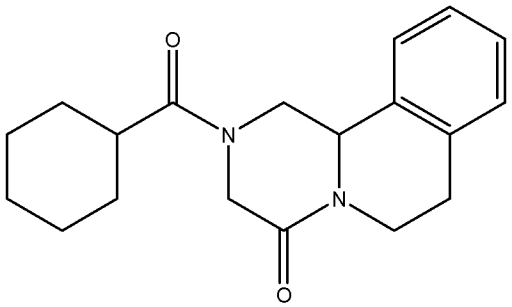
Claims 2 and 11 have been rejected under 35 U.S.C. § 103(a) as unpatentable over the '489 publication in view of the '422 patent, U.S. Patent No. 6,426,333 to Huet et al. ('333 patent) and U.S. Patent No. 6,165,987 ('987 patent) to Harvey. The Office Action asserts that although the '489 publication and the '422 patent do not describe or suggest the use of glycol ether solvents in formulations, it would have been prima facie obvious to modify the teaching of the '489 publication to include glycol ethers based on the teaching of the '333 patent and the '987 patent. Applicants respectfully disagree and traverse the rejection of claims 2 and 11.

The '333 patent to Huet et al. describes spot-on formulations for the treatment or prophylaxis of parasite infestations in animals, which comprise a 1-phenylpyrazole derivative and a ML antiparasitic agent in combination with a carrier and optionally a crystallization inhibitor. As pointed out in the Office Action, the '333 patent describes that the formulations may include a variety of different carriers including several glycol ether solvents. The 1-phenylpyrazole active agents described in the '333 patent have the structure shown below, wherein X may be a nitrogen or an optionally substituted carbon, and variables R_1, R_2, R_4, R_{11} and R_{13} are as described in the patent.



As discussed above, the '489 publication describes that ML active agents are incompatible with levamisole and fairly teaches against combination of the two active agents in a single phase solvent system because of different solubility and stability requirements. The teaching of the '333 patent that a compositions comprising a 1-phenylpyrazole and a ML may include glycol ether solvents in combination with the teachings of the '489 publication and the '422 patent does not suggest the composition recited in the claims. Further, the '333 patent does not provide any motivation to modify the teaching of the '489 publication or the '422 patent to arrive at a stable formulation consisting essentially of levamisole and an avermectin or levamisole and a milbemycin which are dissolved in a pyrrolidone solvent and a glycol ether co-solvent, as recited in claim 2. The fact that the '333 patent teaches that a 1-phenylpyrazole, which is substantially different than levamisole, may be combined with a ML in a solvent system that includes a pyrrolidone solvent and a glycol ether does not suggest the combination of a ML and levamisole in the same solvent system because the '489 publication clearly teaches that a ML and levamisole are not compatible and must be present in different solvents which are immiscible in order to form a stable composition.

The '987 patent to Harvey describes veterinary compositions comprising at least one ML in combination with praziquantel and an organic solvent that is capable of dissolving both active agents. As noted by the Examiner, the '987 patent teaches that ML anthelmintics need to be administered as solutions as their solid forms are poorly adsorbed by the animal. This teaching relates in general to the administration of ML active agents but does not relate to a stable composition comprising both a ML and levamisole. Similarly to the '333 patent and the '422 patent, the '987 patent teaches a composition that contains a ML active agent in combination with an active agent that is structurally distinct from levamisole (shown below).



praziquantel

The teaching of the '987 patent that compositions comprising a ML and praziquantel in a carrier that may include one or more organic solvents that will dissolve the active agents does not teach or suggest the stable composition recited in claim 2 or provide any motivation to modify the teachings of the '489 publication and the '422 patent to arrive at the claimed composition. As discussed above, a teaching that a ML active agent may be combined with a second active agent with a very different structure, which would be expected to have very different properties, in solvent system that includes a pyrrolidone and a glycol ether does not suggest a combination of a ML and levamisole, which the '489 publication teaches are incompatible. Furthermore, the '422 patent alone or in combination with the '333 patent and the '422 patent do not provide motivation to modify the teaching of the '489 publication, which teaches that a ML and levamisole must be in different carriers that are immiscible to achieve acceptable stability, to arrive at the composition of claim 2.

The '987 patent generally describes a method for the treatment of non-human animals with a composition comprising a ML in combination with praziquantel. The efficacy examples described in the '987 patent demonstrate that a composition comprising abamectin alone or abamectin in combination with praziquantel in drench formulations are effective at treating hoggets (sheep) that are infected with *Cooperia* or *Ostertagia*. However, the '987 patent does not teach the use of a ML in combination with levamisole for the treatment of these endoparasites in sheep, much less in cattle, as recited in claim 11. Cattle and sheep are different species with many basic physiological and metabolic differences, and success in the treatment of an endoparasitic infection in one species does not predict that a drug will be safe and effective in the other species. Different species metabolize drugs differently, which may lead to lack of efficacy or dangerous side effects. Furthermore, the use of a combination of praziquantel and a ML in a given formulation does not predict or make obvious that a combination of a ML with a completely different active agent will be effective and safe in the same animal, much less a different species.

As discussed above, stable formulations comprising a ML and levamisole are not taught or suggested by the combination of the '489 publication, the '422 patent, the '333 patent and the '987 patent because the '489 publication teaches that compositions containing a ML and levamisole are unstable unless the two actives are in separate phases. The teachings of the '422 patent, the '333 patent and the '987 patent of combinations of a ML with other distinct active

agents does not suggest the formulation recited in claims 1 or 2. Therefore, since the formulation recited in the claims is not obvious in view of the combined teachings of the cited references, a method to treat cattle infected with *Cooperia* or *Ostertagia* cannot be obvious. Applicants respectfully request withdrawal of the rejection.

Claims 1 and 11 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the '489 publication in view of the '422 patent, and the '987 patent. Applicants respectfully traverse the rejection. As noted above, the combination of the '489 patent and the '422 patent do not teach or suggest the formulation recited in claim 1 because the '489 patent fairly teaches against combining a ML and levamisole in single solvent and a single phase due to stability issues. The teaching of the '987 patent does not correct the deficiency of the '489 publication and the '422 patent because it teaches a composition comprising a ML and a very different active agent (clorsulon), which would be expected to have properties that are very different than those of levamisole. Accordingly, the formulation recited in claim 1 is not obvious in view of the combination of the '489 publication, the '422 patent and the '987 patent.

Since formulation of claim 1 is not obvious over the combination of the '489 publication, the '422 patent and the '987 patent, the method of treating cattle infected with *Cooperia* or *Ostertagia* using this composition is also not obvious in view of the three references. In addition, as noted above, although the '489 patent generally describes a method for the treatment of non-human animals with parasitic infections, the examples demonstrate that compositions comprising a ML and praziquantel are effective against *Cooperia* or *Ostertagia* in sheep, not cattle. The method of claim 11, which requires administration of the formulation of claim 1, which contains a different combination of active agents, to cattle infected with *Cooperia* or *Ostertagia* is not taught or suggested by the '987 patent alone or in combination with the '489 publication and the '422 patent. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

Reconsideration of the claims in view of the remarks provided above is respectfully requested. A Notice of Allowance is earnestly solicited. If the Examiner believes any informalities remain in the application, which may be corrected by Examiner's amendment, or whether any other issues can be resolved by telephone interview, a telephone call with the undersigned is courteously solicited.

The Commissioner is authorized to charge any fee associated with this paper, or credit any overpayment in fees, to Deposit Account No. 50-2354.

Respectfully submitted,
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